Nanogen, Inc.

Briefcase-Sized System for Accurate, Cost-Effective DNA Diagnostics

By 1997, the various tools that used DNA as the basis for diagnostic work were progressing toward the commercialization stage. Several prototypes existed, but none had the crucial combination of small sample preparation cycle times and miniaturized components. Existing processes were labor intensive and required a significant number of additional steps to complete a DNA-based diagnostic workup. Consequently, DNA diagnostic tests cost between $3,000 and $20,000 in 1997 because of the lack of affordable analysis technology and processes. Using cost-shared funds awarded by the Advanced Technology Program (ATP) in May 1997, Nanogen, Inc., sought to develop a briefcase-sized analysis system that could accept standardized, prepared DNA samples and generate accurate diagnostic results at a commercially viable cost of $100 per test. Nanogen's plan was to expand its core DNA analysis microchip technology to the point where the chip could integrate with an entirely portable analysis unit and provide results for any desired DNA sequence. In late 1999, when the ATP-funded project ended, Nanogen had successfully developed a prototype DNA diagnostic machine that reduced sample preparation time from 40 minutes to 10 minutes and reduced the cost to just over $100 per test.

COMPOSITE PERFORMANCE SCORE
(based on a four star rating)
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Research and data for Status Report 96-01-0172 were collected during June 2001 - December 2002.

Diagnostic Methods Are Too Slow and Too Costly

In late 1996, there were products on the market that could analyze 96 gels in parallel, separate the DNA in 90 minutes, and use a computer to read the results directly from the gels. Older technology still on the market took up to six hours for the DNA to separate in the gel. Though the newer technology offered the improvement that was required for diagnostic work, the cost was still too high for widespread use, with DNA diagnostic tests ranging from $3,000 to $20,000 each.

Even with the improvements in DNA diagnostics that had been achieved during the early 1990s, several barriers were still evident in late 1996. First and foremost, no DNA reader existed that could analyze large samples prepared on microchips, detect abnormalities, cross-reference the abnormalities with a database of appropriate DNA sequences, and suggest proper diagnoses. Second, large samples could not be sequenced without time-intensive preparation work and analysis on multiple chips. Third, materials and manpower costs remained too high for chip-based DNA diagnostics to achieve widespread acceptance within the healthcare industry.

These were significant problems since genetic disorders are sometimes caused by multiple genetic abnormalities. In order to ensure an accurate diagnosis, scientists need to sequence large amounts of DNA. Before this ATP-funded project, analyzing large amounts of DNA could not be done on one chip. As a result, DNA diagnostic technology was not as accurate or cost-effective as was required for commercial viability.

Proposed Technology Could Significantly Reduce Costs

Nanogen's proposal to ATP focused on overcoming the technical barriers that stood in the way of a briefcase-sized, portable genetic analysis system that could rapidly, accurately, and inexpensively analyze a genetic sequence. The primary application for the system would

be detecting pathogens or defects for medical diagnostics and epidemiology. The system would replace labor-intensive analysis steps that increased analysis costs significantly more than was necessary. The proposed analysis system would be able to take a standardized sample of any size, fragment and separate the appropriate nucleic acids, and determine where the abnormalities were in the specific genetic code.

The key innovation, in addition to dramatic improvements in sample preparation and analysis, was the creation of a multichip detection and control module to analyze the assay results. The proposed ATP project would significantly extend Nanogen's core abilities to prepare samples and conduct the sequencing in order to handle larger genetic samples quickly, accurately, and inexpensively.

Nanogen's proposal to ATP focused on a briefcase-sized, portable genetic analysis system.

By bringing the cost of DNA-based diagnostics down to a commercially viable target of $100 per test, a successful Nanogen project would create economic benefits for healthcare providers, employers, and patients, as well as positively impact worker productivity and general public health. If DNA diagnostics became less expensive, healthcare providers could administer the more accurate, more efficient tests and could begin preventative treatment immediately. Employers could keep their health costs down and, by providing preventive medical care benefits, could avoid longer term, more serious illnesses in employees. Overall productivity could increase because a healthier population takes fewer sick days, and a general improvement in public health could prolong life.

Technical Risks Forestall Funding

Nanogen's proposed approach involved completely overhauling its central systems and chips in order to integrate them into a new set of hardware and software. The company would have to divert significant resources to merge so many disparate systems, which would lead to a negative impact on other shorter term efforts. As an early- to mid-stage company, Nanogen could not devote the necessary resources to the high-risk integrated technologies needed for a next-generation system. The risk, coupled with the lack of private-sector funding, led Nanogen to submit a proposal to ATP. In 1997, ATP awarded the company $2 million to develop a portable genetic analysis system.

Nanogen Solves Technical Issues with the DNA Diagnostic System

In order to miniaturize the technology and create a briefcase-sized DNA diagnostics system, Nanogen had to improve the sample preparation process and adjust its core chip technology to separate and analyze substantially more DNA. Across the life of the ATP-funded project, Nanogen scientists and engineers worked hard to address these technical shortcomings. By the end of the project, Nanogen had shortened the sample preparation cycle from 40 minutes to 10 minutes by creating a new amplification and preparation system. The company also improved its diagnostic chip so that the chip could handle more prepared samples than it could before the start of the project. Finally, Nanogen adjusted the electric current running through its chip to optimize the process and complete the briefcase-sized DNA diagnostic system.

DNA Diagnostic Product Is Commercialized

Through the ATP-funded project, Nanogen developed a working prototype that accurately sequenced DNA samples. Knowledge gained from that prototype led to the commercialization of the NanoChip™, a chip reader, and a chip loader. The NanoChip™ itself is only 0.7 square centimeters, but up to 109 cell fragments per site on all 99 test-sites can be loaded onto the chip. Even with such an intense load, the chip and the reader can accurately separate, hybridize, and sequence up to 400 base pairs from up to 99 trillion cell fragments. After equipment purchase, the total cost per test is just over $100-significantly less than the $3,000 to $20,000 per test that was charged before this project began.

The entire NanoChip™ Molecular Biology Workstation contains three separate subsystems: (1) a freestanding microchip loader with a fluid-handling subsystem to perform electric addressing of blank microchips in

microchips in preparation for specific types of samples; (2) a highly sensitive, laser-based fluorescence scanner; and (3) computer hardware and software with a graphical user menu. The first and third systems contain significant amounts of knowledge gained during this research project.

The resulting technology reduced costs from a high of $20,000 to about $100 per test and reduced the time needed for sample analysis by 75 percent.

Nanogen scientists published several papers and gave a number of presentations on components within the workstation. The company also disclosed information specific to its technical advances in seven patent applications stemming from this ATP-funded project.

Conclusion

Nanogen set out to create a DNA diagnostic system that could prepare, process, and analyze samples more quickly, more accurately, and less expensively than machines on the market in 1997. ATP cost-shared funding enabled Nanogen to successfully achieve this goal. The resulting technology reduced costs from a high of $20,000 to about $100 per test and reduced the time needed for sample analysis by 75 percent.

PROJECT HIGHLIGHTS
Nanogen, Inc.

Project Title: Briefcase-Sized System for Accurate, Cost-Effective DNA Diagnostics (A Portable Genetic Analysis System)

Project: To develop a portable genetic analysis system that can rapidly and accurately profile a genetic sequence for applications including forensic analysis, battlefield casualty identification, trauma victim identification, diagnostics, and environmental and health monitoring.

Duration: 5/1/1997-9/30/1999
ATP Number: 96-01-0172

Funding (in thousands):

ATP Final Cost	$2,000	51%
Participant Final Cost	1,935	49%
Total	$3,935	

Accomplishments: This highly successful program enabled a biotech startup company to develop a microchip-sized DNA diagnostic system and a briefcase-sized workstation for inexpensive analysis. The company's technology reduced the total cost of tests from a high of $20,000 per test to just over $100. The cost savings resulted from the decreased size, energy, process, and manpower requirements facilitated by the system's automated processes. Nanogen applied for seven patents for this technology; the applications were still pending at the time of the Status Report research.

Commercialization Status: The NanoChip™ Molecular Biology Workstation is the first product line in what Nanogen hopes will be a long series of DNA diagnostic tools. Current capabilities include detecting abnormalities in gene sequences. Future diagnostic applications include entries into the oncology, infectious diseases, and genetic testing markets.

Outlook: As the benefits of the Human Genome Project become more widespread, the market for DNA diagnostic machines will increase substantially. Moreover, as Nanogen endeavors to develop affordable and smaller diagnostic machines for increasingly diverse illnesses and applications, the market will expand. Nanogen created the first stand-alone diagnostic system that could perform inexpensive tests of large DNA samples. Therefore, the outlook for Nanogen, and for the DNA diagnostic industry, is good.

Composite Performance Score: * * *

Number of Employees: 48 employees at project start, 160 as of December 2002.

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